

AMENDMENTS TO THE CLAIMS:

This listing of the claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1. (Currently amended) A multivalent composition for active idiotype immunotherapy comprising at least two recombinant protein molecules comprising variable regions of at least two immunoglobulin molecules derived from quasi-clonal B-cell lymphoma cells, wherein said at least two variable regions comprise are derived from nucleic acid encoding said at least two recombinant immunoglobulin molecules, and wherein said at least two immunoglobulin molecules that differ by at least one idiotope.

2. (Canceled)

3. (Currently amended) The composition of Claim 1, wherein said recombinant protein immunoglobulin molecules are covalently linked to an immune-enhancing cytokine.

4. (Previously presented) The composition of Claim 3, wherein said cytokine is selected from the group consisting of granulocyte-macrophage colony stimulating factor, interleukin-2 and interleukin-4.

5. (Currently amended) The composition of Claim 1 further comprising at least one pharmaceutically acceptable excipient.

6. (Previously presented) The composition of Claim 1 further comprising an adjuvant.

7-24. (canceled)

25. (Currently amended) A multivalent composition for active idiotype immunotherapy produced according to a method comprising:

a) providing:

- i) malignant B cells isolated from a patient having a quasi-clonal B-cell lymphoma;
- ii) an expression vector;
- iii) an amplification vector comprising a recombinant oligonucleotide

having a sequence encoding a first inhibitable enzyme operably linked to a heterologous promoter; and

iv) a T lymphoid parent cell line;

b) isolating nucleic acid from said malignant cells, said nucleic acid comprising nucleotide sequences selected from the group consisting of nucleotide sequences encoding at least one V_H region and at least one two V_L region regions, nucleotide sequences encoding at least two V_H regions and at least one V_L region, and nucleotide sequences encoding at least two V_H regions and at least two V_L regions, wherein said at least two V_L regions differ by at least one idiotope, wherein said at least two V_H regions differ by at least one idiotope, and wherein said V_H and V_L regions are derived from immunoglobulin molecules expressed by said malignant cells;

c) inserting said nucleotide sequences encoding said V_H and V_L regions into said expression vector ;

d) introducing said expression vector and said amplification vector into said parent cell line to generate one or more transformed cells;

e) growing said transformed cells in a first aqueous solution containing an inhibitor capable of inhibiting said first inhibitable enzyme wherein the concentration of said inhibitor present in said first aqueous solution is sufficient to prevent growth of said parent cell line; and

f) identifying a transformed cell capable of growth in said first aqueous solution, wherein said transformed cell capable of growth expresses said V_H and V_L regions wherein V_H and V_L regions comprise a protein molecule useful as said active idiotype immunotherapy.

26. (Previously presented) The composition of Claim 25, wherein nucleotide sequences encoding said V_H and V_L regions comprise at least two V_H and at least one V_L regions.

27. (Previously presented) The composition of Claim 25, wherein nucleotide sequences encoding said V_H and V_L regions comprise at least one V_H and at least two V_L regions.

28. (Currently amended) A multivalent composition for active idiotype immunotherapy produced according to a method comprising:

- a) providing:
- i) malignant B cells isolated from a patient having a quasi-clonal B-cell lymphoma;

- ii) an expression vector;
 - iii) an amplification vector comprising a first recombinant oligonucleotide having a sequence encoding a first inhibitable enzyme operably linked to a heterologous promoter;
 - iv) a selection vector comprising a second recombinant oligonucleotide having a sequence which encodes a selectable gene product; and
 - v) a T lymphoid parent cell line;
- b) isolating nucleic acid from said malignant cells, said nucleic acid comprising nucleotide sequences selected from the group consisting of nucleotide sequences encoding at least one V_H region and at least one two V_L region regions, nucleotide sequences encoding at least two V_H regions and at least one V_L region, and nucleotide sequences encoding at least two V_H regions and at least two V_L regions, wherein said at least two V_L regions differ by at least one idiotope, wherein said at least two V_H regions differ by at least on idiotope, and wherein said V_H and V_L regions are derived from immunoglobulin molecules expressed by said malignant cells;
- c) inserting said nucleotide sequences encoding said V_H and V_L regions into said expression vector;
- d) introducing said expression vector, said amplification vector and said selection vector into said parent cell line to generate transformed cells;
- e) introducing said transformed cells into a first aqueous solution, said first aqueous solution requiring the expression of said selectable gene product for growth of said transformed cells;
- f) identifying at least one transformed cell capable of growth in said first aqueous solution;
- g) introducing said transformed cell capable of growth in said first aqueous medium into a second aqueous solution, said second aqueous solution comprising an inhibitor capable of inhibiting said first inhibitable enzyme, wherein the concentration of said inhibitor present in said second aqueous solution is sufficient to prevent growth of said parent cell line; and
- h) identifying at least one transformed cell capable of growth in said second aqueous solution, wherein said transformed cell capable of growth expresses said V_H and V_L regions wherein said V_H and V_L regions comprise a protein molecule.

29. (Currently amended) A multivalent composition for active idiotype immunotherapy

produced according to a method comprising:

- a) providing:
 - i) malignant B cells isolated from a patient having a quasi-clonal B-cell lymphoma;
 - ii) an expression vector;
 - iii) an amplification vector comprising a first recombinant oligonucleotide having a sequence encoding a first inhibitable enzyme operably linked to a heterologous promoter;
 - iv) a selection vector comprising a second recombinant oligonucleotide having a sequence which encodes a selectable gene product; and
 - v) a T lymphoid parent cell line;
- b) isolating nucleic acid from said malignant cells, said nucleic acid comprising nucleotide sequences selected from the group consisting of nucleotide sequences encoding at least one V_H region and at least one two V_L region regions, nucleotide sequences encoding at least two V_H regions and at least one V_L region, and nucleotide sequences encoding at least two V_H regions and at least two V_L regions, wherein said at least two V_L regions differ by at least one idiotope, wherein said at least two V_H regions differ by at least one idiotope, and wherein said V_H and V_L regions are derived from immunoglobulin molecules expressed by said malignant cells;
- c) inserting said nucleotide sequences encoding said V_H and V_L regions into said expression vector;
- d) introducing said expression vector, said amplification vector and said selection vector into said parent cell line to generate transformed cells;
- e) introducing said transformed cells into a first aqueous solution, said first aqueous solution requiring the expression of said selectable gene product for growth of said transformed cells;
- f) identifying at least one individual clone of transformed cells capable of growth in said first aqueous solution;
- g) introducing said individual clone capable of growth in said first aqueous solution into a second aqueous solution, said second aqueous solution comprising an inhibitor capable of inhibiting said first inhibitable enzyme, wherein the concentration of said inhibitor present in said first aqueous solution is sufficient to prevent growth of said parent cell line; and

h) identifying at least one individual clone capable of growth in said second aqueous solution, wherein said clone capable of growth expresses said V_H and V_L regions wherein said V_H and V_L regions comprise a protein molecule.

30. (Currently amended) A multivalent composition for active idiotype immunotherapy comprising at least two recombinant variable regions of immunoglobulin molecules derived from quasi-clonal B-cell lymphoma cells from a patient, wherein said cells express at least two different immunoglobulin molecules, said immunoglobulin molecules differing by at least one idiotope, wherein said at least two recombinant variable regions of immunoglobulin molecules are derived by a method comprising the step of amplifying cDNA for said variable regions from mRNA from said B-cell lymphoma cells using amplification primers complementary to conserved sequences flanking said variable regions.

31. (Currently amended) The composition of Claim 1, wherein said recombinant protein immunoglobulin molecules are conjugated to a foreign carrier protein.

32. (Previously presented) The composition of Claim 31, wherein said foreign carrier protein comprises keyhole limpet hemocyanin.